



## Evidence of brain network aberration in healthy subjects with urban upbringing – A multimodal DTI and VBM study

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### ABSTRACT

City living represents not only the allegory of modern life, but also – due to attractive living conditions, employment and infrastructure – a crucial reality for a growing portion of the global society. Regarding the remarkable increase of the schizophrenia incidence in individuals exposed to an urban environment during upbringing the understanding of responsible pathogenetic mechanisms is important. Schizophrenia has been conceptualized as a disorder of brain dysconnectivity. We investigated the association between urban upbringing and gray matter as well as white matter in a large sample of healthy subjects ( $n = 290$ ). Voxelwise analyses revealed a strong inverse correlation of early life urbanicity and gray matter volume of the bilateral dorsolateral prefrontal cortices (DLPFC) and the right inferior parietal lobe (IPL) as well as the white matter characteristics in the left superior longitudinal fasciculus (SLF). A positive correlation was found for the gray matter volume of the left precuneus. These results may point to an altered brain development associated with urban upbringing, which not only affects single brain regions but a fronto-parietal network. Considering a DLPFC susceptibility to stress, our findings support the hypothesis of the pathogenetic role of social stress in an urban environment.

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### 1. Introduction

Urban upbringing has been consistently associated with an elevated risk for non-affective psychosis (Mortensen et al., 1999; March et al., 2008; Vassos et al., 2012). There is evidence for an existing dose-response relationship between urbanicity during upbringing and schizophrenia risk later in life that is indicating a certain vulnerability of the developing brain to influences of the urban environment (Pedersen and Mortensen, 2001). These factors interfere mainly during the first 15 years of life, contributing to an about 2-fold increase of the schizophrenia risk in the most urbanized regions (Vassos et al., 2012). Factors such as cannabis use (more common in urban areas (Kuepper et al., 2011)), microbial pathogens (Brown et al., 2000) and toxins (Pedersen et al., 2004) have been hypothesized to play a role in this relationship. However, while they are unlikely to function as main effects, social stress is attracting growing attention.

Structures of city life, characterized by a complex social environment that is on the one hand hyper- and on the other hyposocial, are demanding a high degree of adaption of individuals (Downey, 2016). This social environment bears the risk for social defeat, or ambiguous communication which are strongly associated with the perception of stress (Selten

and Cantor-Graae, 2007). Stress in general, and especially social stress, is affecting mental health (Nuechterlein and Dawson, 1984; van Os et al., 2005) and can lead – particularly when an individual is exposed to stress during upbringing – to morphological changes, predominantly in the prefrontal cortex (Arnsten, 2009). Social stress in combination with impaired capacities of coping due to a social environment lacking participation and trust has been hypothesized to account for increased incidences of mental disorders in cities (Abbott, 2012).

Aberrant structural brain connectivity in patients with schizophrenia are prominent, but heterogeneous. Most consistent findings are gray matter volume reductions in frontal and temporal regions as well as reductions in the white matter microstructure, especially reduced fractional anisotropy in fronto-temporal fiber tracts (Dietsche et al., 2017). Identifying morphologic correlates of environmental risk factors is a promising approach for a better understanding of the pathophysiology of schizophrenia. Previously, a functional MRI-study showed differences in social stress processing of healthy subjects grown up in cities – regardless of the current residence. Urban upbringing was associated with higher activities in the perigenual anterior cingulate cortex which is pointing to a certain vulnerability of cerebral stress regulation structures during childhood and adolescence (Lederbogen et al., 2011). Recent findings showing a reduced gray matter volume of the dorsolateral prefrontal cortex (DLPFC) in healthy individuals exposed to early life urbanicity fit into this context (Haddad et al., 2015).

On the basis of the disconnection hypothesis of schizophrenia (Friston and Frith, 1995; Wernicke, 1906) and respecting the relevance

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of brain networks for physiological brain functioning, we aimed to examine the effect of urban upbringing on gray and white matter structures. It was hypothesized that early life urbanicity is associated with (i) reduced gray matter volume in prefrontal and temporal areas and (ii) reduced white matter microstructure (fractional anisotropy), particularly in fiber tracts connecting prefrontal areas.

## 2. Material and methods

### 2.1. Subjects

Two hundred ninety subjects (age: M 28.48, SD  $\pm$  8.28 years; gender: 158 men, 132 women; education: M 13.88, SD  $\pm$  2.75) of Western- or Middle-European ancestry were included in our study. Structured clinical interviews for DSM-IV (Wittchen et al., 1997) were performed by trained psychologists to exclude individuals with a history of a mental disorder (incl. Drug abuse). Moreover, none of the included participants reported taking psychiatric medication or had current or past severe major medical or neurological issues. Further inclusion criteria were an age between 18 and 60 years, IQ > 85 points assessed with a neuropsychological battery, as well as general MRI inclusion criteria (e.g. no tattoos, no pregnancy, no metal or medical objects in the body). Subjects were recruited via postings, advertisements or Email lists in Marburg (Germany), which has about 76.000 inhabitants. However, the sample consists of a slightly higher portion of well-educated and younger than low educated and older subjects, which does not depict a representative sample of the population of Marburg. After a complete description of the procedure, all participants gave written informed consent. The protocol was approved by the local ethics committee according to the declaration of Helsinki."

### 2.2. Assessment of urban upbringing

Subjects completed a questionnaire regarding their upbringing. For each year until the age of 15 years, one point was given for rural areas with 10.000 habitants or less, two points were given for upbringing in cities with 10.001–100.000 citizens and three points were given for each year lived in a city with >100.000 citizens. Thus, urbanicity-scores ranged from 15 to 45 (cf. Pedersen and Mortensen, 2001).

### 2.3. Structural image acquisition and analysis

For all data sets ( $n = 290$ ), imaging was performed on a 3-Tesla Trio MR scanner (Siemens Medical Systems, Erlangen, Germany) at the Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Germany. Head movements were minimized by tightly fixating the head with cushions during the scanning procedure. After a localizer sequence, a high-resolution T1-weighted volume data set of the whole brain was acquired using an MR-RAGE sequence. Slices covered the whole brain and were positioned transaxially parallel to the AC-PC line. Acquisition matrix was 256\*256, 176 slices, thickness 1 mm, acquisition parameters were TE 2.26, TR 1900, flip angle 9°, distance factor 50%, field of view 256 mm, resulting in isotropic voxels of  $1 \times 1 \times 1 \text{ mm}^3$  size.

#### 2.3.1. VBM

All data sets were pre-processed with standard (default) parameters of the VBM8-Toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) in SPM8. Images were inspected for segmentation and normalization, and sample homogeneity was controlled using covariance statistics. All volumes outside two standard deviations of the mean were discarded from further analyses. In a final step, images were smoothed with an 8 mm Gaussian filter. This resulted in smoothed modulated normalized data representing gray matter volume for the statistical analysis. A multiple regression analysis was calculated in SPM8. Scores for urban upbringing, age and gender were entered in the model. To restrict analyses to areas

with a gray matter probability of 0.2, an absolute threshold of 0.2 was set up. Contrasts were calculated for the positive and negative effect of urban upbringing and results were thresholded at  $p < 0.001$  uncorrected. To correct for multiple comparisons within a search volume, we applied a cluster extend threshold determined by Monte Carlo (Slotnick et al., 2003). For a threshold at the voxel level  $p = 0.001$  and spatial properties as present in this study, 10.000 simulations resulted in an extent threshold of 43 resampled voxels. This procedure prevented a false positive rate above 5% due to multiple testing.

#### 2.3.2. DTI

Diffusion tensor imaging data for  $n = 222$  subjects were available and acquired as described in the following: Diffusion weighted images (DWI) were acquired with a single-shot echo planar imaging (EPI) sequence (repetition time 7800 ms, echo time 90 ms, 2.5 mm isotropic resolution, 56 slices in interleaved order, no gap, 30 gradient directions, parallel imaging (GRAPPA) with factor 2, bandwidth 1502 Hz/pixel, phase encoding direction AC-PC). For each participant two subsequent sets of DWI and five interleaved non-weighted images (b-values 0 and 1000 s/mm<sup>2</sup>) were acquired. Acquisition time for each participant for all DTI data was in total about 12 min. For a more detailed description of the image acquisition and data quality control see Dietsche et al. (2014).

Analysis of DTI data was performed using the FMRIB Software Library (FSL version 5.02, Oxford, U.K., <http://www.fmrib.ox.ac.uk/fsl/>). DTI pre-processing was performed as follows: 1) head motion and eddy current correction, 2) removal of non-brain tissue from an image of the whole head and 3) fitting of diffusion tensor model at each voxel. All FA images were visually checked for artifacts, intensity range problems and general data quality. Voxelwise statistical was performed using tract-based spatial statistics (TBSS) version 1.2 implemented in FSL according to the standard procedure (Smith et al., 2006): 1) non-linear registration of all fractional anisotropy (FA) images  $1 \times 1 \times 1 \text{ mm}^3$  Montreal Neurological Institute (MNI) space 2) creation of the mean FA image of all participants and 3) creation of a mean skeleton projection of all subjects FA data onto the mean FA skeleton, setting a non-maximum-suppression FA threshold to  $\geq 0.3$ . A general linear model (GLM) was performed using the FSL Randomise tool, entering scores for urban upbringing, age and gender into the model. Each contrast (positive and negative effect of urban upbringing) was performed on a whole brain level according to permutation-based non-parametric inference with 10.000 random permutations and a significance level of  $p < 0.05$  family wise error (FWE) corrected using threshold-free cluster enhancement (TFCE) approach (Smith and Nichols, 2009).

#### 2.3.3. Post-hoc analysis

Furthermore, additional regression analysis was performed testing the influence of potential confounding factors such as years of education, intelligence and current residence.

## 3. Results

### 3.1. VBM – results

The multiple regression analysis in SPM8 revealed an inverse correlation of urban upbringing and gray matter volume in the bilateral DLPFC (MNI coordinates: -45, 9, 30;  $T = 3.97$ , cluster extent = 255 voxels; MNI coordinates: 58, 16, 13;  $T = 3.47$ , cluster extent = 102 voxels) and the right inferior parietal lobe (IPL) (MNI coordinates: 40, -46, 46;  $T = 3.64$ , cluster extent = 124 voxels). A positive correlation was found for the gray matter volume of the left precuneus (MNI coordinates: -6, -63, 55;  $T = 4.04$ , cluster extent = 114 voxels) (see Table 1 and Fig. 1).

**Table 1**  
Intercorrelation of gray and white matter parameters.

	Prec <sup>a</sup>	IDLPFC <sup>a</sup>	rDLPFC <sup>a</sup>	rIPL <sup>a</sup>	SLF <sup>b</sup>
Urbanicity	<b>0.24***</b>	<b>-0.22***</b>	-0.18**	-0.21***	<b>-0.26***</b>
Prec	–	0.05	0.09	0.14*	-0.05
IDLPFC	–	–	<b>0.31***</b>	<b>0.29***</b>	0.16*
rDLPFC	–	–	–	<b>0.22***</b>	0.12
rIPL	–	–	–	–	0.00

Coefficients in bold survived Bonferroni correction.

Annotations:

<sup>a</sup> VBM.

<sup>b</sup> DTI, l = left, r = right; Prec = precuneus, DLPFC = dorsolateral prefrontal cortex, IPL = inferior parietal lobe, SLF = superior longitudinal fasciculus; Beta-values for VBM and FA-values for DTI were extracted from each significant cluster.

\*  $p < 0.05$ .

\*\*  $p < 0.01$ .

\*\*\*  $p < 0.001$ .

### 3.2. DTI – results

The voxelwise analysis revealed a negative relationship between urban upbringing and white matter microstructure in a widespread cluster (736 voxels, MNI coordinates: -25, -24, 42;  $p = 0.03$ , FWE-corrected) mainly comprising the left superior longitudinal fasciculus (SLF), left corticospinal tract (CT) and left superior corona radiata (SCR) (see Table 1 and Fig. 2). There was no region with a significant positive relationship between urban upbringing and white matter microstructure ( $p > 0.84$ ).

### 3.3. Post-hoc analysis

There was no significant relationship between the tested potential confounding variables such as years of education, intelligence as well as current residence with brain structure. In addition, we calculated the effect sizes of the relationship of urban upbringing and brain structure: SLF:  $r = 0.26$ ; left DLPFC:  $r = 0.20$ ; right DLPFC:  $r = 0.16$ ; right IPL:  $r = 0.20$ ; left precuneus:  $r = 0.24$ .

## 4. Discussion

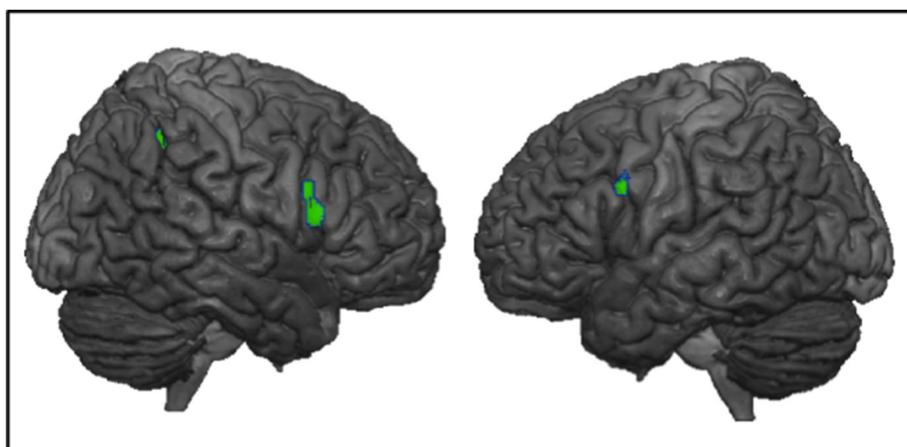
The purpose of this study was to investigate the association between urban upbringing (until the age of 15 years) with gray matter volume and white matter microstructure in a large sample of healthy subjects. An inverse relationship between early life urbanicity and gray matter volume of the bilateral DLPFC and of the right IPL as well as white matter anisotropy of the left SLF, the left CT and the left SCR was apparent. A

positive association between urban upbringing was evident for the gray matter volume of the left precuneus.

Urban upbringing is a widely-accepted risk factor for non-affective psychosis. Consistent with prior work our findings point to a pathophysiological mechanism by which urban upbringing may affect brain maturation with a consecutively increased risk for schizophrenia. Volume reductions of the DLPFC have already been reported in a similar study to ours (Haddad et al., 2015) and increase confidence in the present findings. They are in line with findings in subjects at high risk of schizophrenia (Meisenzahl et al., 2008) and in first episode schizophrenia (Ellison-Wright et al., 2008). The DLPFC is massively connected with other areas, essential for working memory and adaptive decision making, among others. It is extremely sensitive to the negative effects of stress – especially to non-controllable stress (Arnsten, 2009). As shown in another study, social stress is generally evaluated as the most unpleasant form of stress, which in context may provide an indication for a core feature of the risk factor urbanicity (Shively et al., 2009).

For more than a century researchers have been trying to attribute the pathogenesis of schizophrenia to specific morphologic correlates (Torrey, 2007). The growing explanatory potential of neurosciences giving insights in the neuronal principles of psychological functions plays a key role in understanding the pathogenesis of psychiatric diseases.

The functional connectivity of brain regions that are forming different brain networks is indispensable for physiologic brain functions. A disruption of this connectivity resulting in a disturbed communication within such networks is a major cause for the pathogenesis of schizophrenia (Davis et al., 2003). Based on that research we investigated the effect of the risk factor urban upbringing on brain architecture and found indications for a disturbed fronto-parietal network. Besides the DLPFC volume, the gray matter volume of the right IPL was also negatively correlated to urban upbringing. Additionally, it showed an intercorrelation with the gray matter volume of the right DLPFC. The IPL, a brain region on the lateral pole of the parietal lobe, is involved in several brain functions which are impaired in schizophrenia – sensory integration, body image and concept of self (Torrey, 2007). Reduced IPL volume has been found in schizophrenia patients (Kubicki et al., 2002; Zhou et al., 2007). Functional connectivity of these prefrontal and parietal regions is facilitated by a major association tract, the SLF (Preuss and Goldman-Rakic, 1989; Karlsgodt et al., 2008). Microstructural changes of the SLF are a common morphologic correlate of schizophrenia (Bopp et al., 2017). Karlsgodt and colleagues described a correlation of white matter changes in the left SLF and the performance of a verbal working memory task in early stages of schizophrenia (Karlsgodt et al., 2008). In the present study, microstructural changes of the left SLF were negatively correlated with urban upbringing and intercorrelated with the gray matter volume of the left DLPFC. These findings suggest an altered connectivity of the fronto-parietal network



**Fig. 1.** Negative correlation of urban upbringing score and gray matter volume in the bilateral DLPFC and the right IPL ( $p < 0.001$ , unc., cluster extent  $> 50$  voxels).

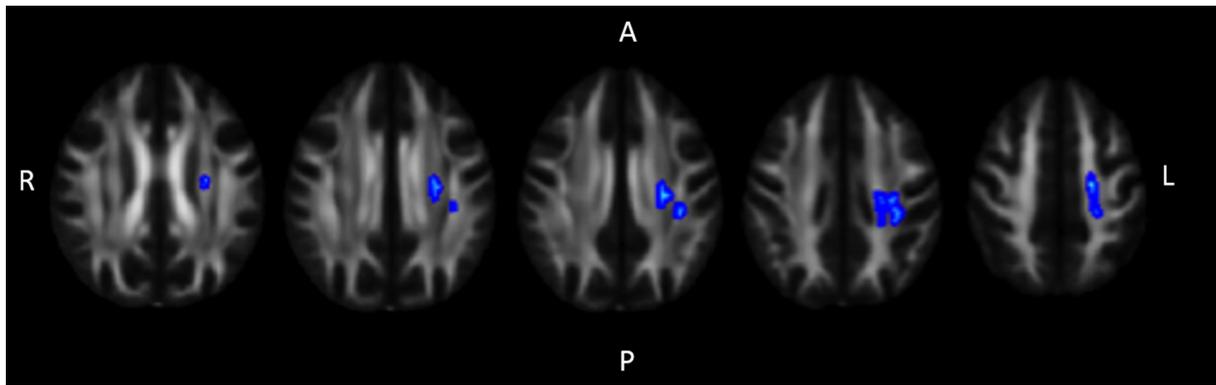


Fig. 2. Negative correlation of urban upbringing score and fractional anisotropy in the left SLF, CT and SCR ( $p < 0.05$ , FWE corrected).

and point to a mutual interference of gray and white matter's structural properties. They support the hypothesis of a disturbed neuronal maturation process in subjects exposed to early life urbanicity. Equally, the associated microstructural changes in the CT, a large efferent fiber tract, support this hypothesis. A study with adolescent-onset schizophrenic patients showed a delayed maturation process of the CT in early-onset schizophrenia (Douaud et al., 2007).

A potential compensatory mechanism to balance the impaired connectivity of the fronto-parietal network could be an explanation for the increased gray matter volume of the precuneus in subjects growing up in urban areas. A redeeming role of this structure in fronto-parietal impairment has been hypothesized previously. Higher perfusion of the precuneus in subjects with paranoid schizophrenia was associated with preserved awareness of their illness and was suggested to be predictive for outcome (Faget-Agius et al., 2012). The precuneus, part of the medial parietal cortex, is a major association area that is functionally connected to the fronto-parietal network and is playing a key role in self-consciousness. As shown in functional MRI studies, the precuneus is notably involved in self-processing (Cavanna and Trimble, 2006), e.g. self-related episodic memory retrieval (Tulving et al., 1994; Shallice et al., 1994), self-referential judgement (Kircher et al., 2000), first- versus third- person perspective taking (Vogeley et al., 2001) and emotional intelligence (social cognition and empathy) (Farrow et al., 2001). In addition, the precuneus is part of the default mode network (DMN), a set of brain regions that is activated during the resting state of the brain. It is implicated in self-referential processing and was found to be hypoactive in schizophrenic patients (Kühn and Gallinat, 2013). Gray matter volume reductions of the precuneus were found in schizophrenia (Borgwardt et al., 2008). The functional properties of the precuneus contribute to a successful social adaptation and may facilitate coping mechanisms in the urban environment. Further research including functional imaging is needed to evaluate this hypothesis.

Despite the large sample and promising findings, the interpretations of the results remain speculative and cannot explain any causality. To assess urban upbringing, we used a classification based on previous epidemiological surveys which quantifies the population size of a rural area, town and city (Pedersen and Mortensen, 2001). This classification is taking into account that humans are especially prone to urban exposure considering neurodevelopmental maturation within the first fifteen years of life (Pedersen and Mortensen, 2001). Regarding the retrospective character of the present study design, the upbringing questionnaire was vulnerable to recall biases: subjects were asked to name the rural area, town or city where they grew up. To minimize mistakes regarding the population size back in time, we reviewed and checked subsequently the accuracy of the subjects' data. Nonetheless, the population size is a vague proxy for underlying finer grained sub-factors of the black box urbanicity. In their meta-analysis Krabbendam and van Os (2005) included 10 studies with different approaches of quantifying

urbanicity: (i) by the number of people relative to the area surface, (ii) by the number of addresses relative to area surface and (iii) by the absolute population counts of cities. They revealed that the rate of schizophrenia in the (differently defined) urban areas is about double compared to the (differently defined) rural areas (Krabbendam and van Os, 2005). In our study we used a categorization system applied in epidemiological research (Pedersen and Mortensen, 2001) and of previous neuroimaging studies (Haddad et al., 2015; Lederbogen et al., 2011). For future work it would be worthwhile to respect inner city contrasts as categories of examination. However, in our study we did unfortunately not have the possibility to do so. Moreover, our sample is not representative of the population of Marburg, which limits the generalizability of our results. Even our results fit well in the existing literature to urbanicity and stress, further research including methods to quantify stress exposure in urban upbringing are needed. Additionally, to minimize confounding factors it would be useful to control for the actual stress-level of the subjects in future studies. To prevent confounding by disorder- or medication-related factors we limited our analysis to healthy subjects. However, it cannot be ruled out that the effect of urban upbringing on brain development differs in subjects who suffer from schizophrenia later in life. Moreover, we showed that years of education, intelligence and current do not influence the association between urban upbringing and brain structure. However, we cannot rule out further confounding factors we did not collect. To our knowledge the present study is the first to investigate the effect of urban upbringing on gray as well as white matter. Thus, our findings extend previous work and underpin the participation of brain-networks rather than single regions associated with urban upbringing. A combination of structural and functional imaging could give more insight in potential differences in brain functioning.

## 5. Conclusion

In summary, urban upbringing is linked to morphological changes in gray and white matter structures, such as DLPFC, IPL, precuneus and SLF. These results mirror those found in (first episode) schizophrenia. Our findings point to an altered connectivity of brain networks, which are evident in healthy subjects exposed to the risk factor early life urbanicity and highlight childhood and adolescence as sensitive periods for brain development.

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## Contributors

BD, SL and AK undertook the data analysis and wrote the manuscript. BD and SL acquired the data. AK and TK designed the study and wrote the study protocol. UD and TK provided intellectual input. UD and TK supervised the data analysis. TK provided infrastructure. All authors critically revised the manuscript. All authors contributed to and have approved the final manuscript.

## Conflict of interest

All authors report no conflict of interest.

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